

WE CLAIM:

1. A composition for injectable delivery of osteogenic proteins comprising an osteogenic protein and a hyaluronic acid ester, said composition being in the form of a cylindrical rod suitable for injecting or implanting in solid state into a body.
2. The composition of claim 1, wherein the osteogenic protein is selected from the group consisting of members of the bone morphogenic protein (BMP) family.
3. The composition of claim 2, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-10, BMP-12 and BMP-13.
4. The composition of claim 2, wherein the osteogenic protein is BMP-2 or BMP-6.
5. The composition of claim 1, further comprising a bone resorption inhibitor.
6. The composition of claim 5, wherein the bone resorption inhibitor is a bisphosphonate.
7. The composition of claim 6, wherein the bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, EB-1053, etidronates, ibandronate, neridronate, olpadronate, pamidronate, risedronate, tiludronate, YH 529, zolendronate, and pharmaceutically acceptable salts, esters, acids, and mixtures thereof.
8. The composition of claim 1, wherein the hyaluronic acid ester comprising from about 50 percent to about 100 percent hyaluronic acid esterification.

9. The composition of claim 1, wherein the hyaluronic acid ester is a cross-linked hyaluronic acid.
10. The composition of claim 1, further comprising an excipient selected from the group consisting of pharmaceutically acceptable salts, polysaccharides, peptides, proteins, amino acids, synthetic polymers, natural polymers, and surfactants.
11. The composition of claim 1, further comprising a bone resorption inhibitor and an excipient selected from the group consisting of pharmaceutically acceptable salts, polysaccharides, peptides, proteins, amino acids, synthetic polymers, natural polymers, and surfactants.
12. The composition of claim 1, wherein the diameter of said cylindrical rod is between about 0.5 to 1.5 mm.
13. The composition of claim 1, wherein the length of said cylindrical rod is between about 2 cm and about 5 cm.
14. A composition for treating osteoporotic bone comprising an osteogenic protein and a hyaluronic acid, which is prepared by a process comprising the steps of:
 - (a) mixing the osteogenic protein and the hyaluronic acid ester to form an osteogenic mixture; and
 - (b) forming and drying the osteogenic mixture into a cylindrical rod suitable for injecting or implanting in solid state into a body.
15. The composition of claim 14, wherein the step of mixing comprises mixing the osteogenic protein and hyaluronic acid ester with a bisphosphonate.
16. The composition of claim 14, wherein the step of mixing comprises mixing the osteogenic protein and hyaluronic acid ester with an excipient

selected from the group consisting of pharmaceutically acceptable salts, polysaccharides, peptides, proteins, amino acids, synthetic polymers, natural polymers, and surfactants.

17. The composition of claim 14, wherein the step of mixing comprises mixing the osteogenic protein and hyaluronic acid ester with a bisphosphonate and an excipient selected from the group consisting of pharmaceutically acceptable salts, polysaccharides, peptides, proteins, amino acids, synthetic polymers, natural polymers, and surfactants.
18. The composition of claim 14, wherein the hyaluronic acid ester is prepared by hydration or solubilization of insoluble or partially soluble particles, films, fibers, non-woven pads, or sponges of hyaluronic acid benzyl esters in water, an organic solvent or an aqueous buffer.
19. The composition of claim 14, wherein the step of mixing comprises mixing the osteogenic protein and hyaluronic acid ester with a bisphosphonate and an excipient selected from the group consisting of pharmaceutically acceptable salts, polysaccharides, peptides, proteins, amino acids, synthetic polymers, natural polymers, and surfactants.
20. The composition of claim 14, wherein the osteogenic protein is selected from the group consisting of members of the bone morphogenic protein (BMP) family.
21. The composition of claim 14, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-10, BMP-12 and BMP-13.
22. The composition of claim 14, wherein the osteogenic protein is BMP-2 or BMP-6.

23. The composition of claim 15, wherein the bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, EB-1053, etidronate, ibandronate, neridronate, olpadronate, pamidronate, risedronate, tiludronate, YH 529, zolendronate, and pharmaceutically acceptable salts, esters, acids, and mixtures thereof.
24. The composition of claim 14, wherein the step of mixing comprises mixing the osteogenic protein and hyaluronic acid ester with a solvent; and wherein the step of forming and drying the osteogenic mixture into a cylindrical rod comprise extruding the osteogenic mixture in a nonsolvent.
25. The composition of claim 18, where in the step of forming and drying the osteogenic mixture comprises
 - (i) extruding the osteogenic mixture in a nonsolvent, or
 - (ii) extruding the osteogenic mixture into air and drying.
26. The composition of claim 25, wherein the nonsolvent is ethanol or water.
27. The composition of claim 14, wherein the diameter of said cylindrical rod is between about 0.5 to 1.5 mm.
28. The composition of claim 14, wherein the length of said cylindrical rod is about 2 cm to about 5 cm.
29. A method for preparing an injectable, rod-shaped, sustained-release preparation comprising an osteogenic protein and a hyaluronic acid ester, which comprises:
 - (a) mixing the osteogenic protein with the hyaluronic acid ester and an excipient selected from the group consisting of pharmaceutically acceptable salts, polysaccharides, peptides, proteins, amino acids, synthetic polymers, natural polymers, and surfactants to

produce an osteogenic mixture comprising the hyaluronic acid ester in an amount of between about 1 to about 50 (w/v) percent;

(b) molding the osteogenic mixture to form a rod-shaped product; and

(c) drying the rod-shaped product from step (b).

30. The method of claim 29, wherein step (a) includes the solubilization of the hyaluronic acid ester into organic solvent.

31. The method of claim 29, wherein step (a) includes the hydration of the hyaluronic acid ester into aqueous buffer.

32. The method of claim 29, wherein the hyaluronic acid ester in step (a) is between about 10 to about 25 (w/v) percent.

33. The method of claim 29, wherein said molding in step (b) comprises
(i) extruding the osteogenic mixture in a nonsolvent, or
(ii) extruding the osteogenic mixture into air and drying.

34. The method of claim 29, wherein the osteogenic protein is selected from the group consisting of members of the bone morphogenic protein (BMP) family.

35. The method of claim 32, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-10, BMP-12 and BMP-13.

36. The method of claim 32, wherein the osteogenic protein is BMP-2 or BMP-6.

37. The method of claim 29, wherein the mixing in step (b) further comprises mixing the osteogenic protein, hyaluronic acid ester and excipient with a bisphosphonate.

38. The method of claim 35, wherein the bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, EB-1053, etidronate, ibandronate, neridronate, olpadronate, pamidronate, risedronate, tiludronate, YH 529, zolendronate, and pharmaceutically acceptable salts, esters, acids, and mixtures thereof.
39. The method of claim 29, wherein the hyaluronic acid ester comprises from about 50 percent to about 100 percent hyaluronic acid esterification.
40. A method for preparing an injectable sustained-release preparation comprising an osteogenic protein and a hyaluronan-based material, which comprises:
 - (a) admixing the osteogenic protein with the hyaluronan-based material to form an admixture;
 - (b) compressing the admixture from step (a) to form a dense osteogenic admixture; and
 - (c) forming the dense osteogenic admixture from step (b) into a solid cylindrical rod suitable for injecting or implanting into a body.
41. The method of claim 38, wherein said forming in step (c) consists of extruding, pressing, molding, boring or cutting to form a cylindrical rod with a diameter of between 0.5 to about 1.5 mm.
42. The method of claim 38, wherein the admixing in step (a) comprises admixing the osteogenic protein and hyaluronan-based material with an excipient selected from the group consisting of pharmaceutically acceptable salts, polysaccharides, peptides, proteins, amino acids, synthetic polymers, natural polymers, and surfactants.
43. The method of claim 38, wherein the admixing in step (a) comprises admixing the osteogenic protein and hyaluronan-based material with a bisphosphonate.

44. The method of claim 39, wherein the osteogenic protein is selected from the group consisting of members of the bone morphogenic protein (BMP) family.
45. The method of claim 38, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-10, BMP-12 and BMP-13.
46. The method of claim 38, wherein the osteogenic protein is BMP-2 or BMP-6.
47. The method of claim 41, wherein the bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, EB-1053, etidronate, ibandronate, neridronate, olpadronate, pamidronate, risedronate, tiludronate, YH 529, zolendronate, and pharmaceutically acceptable salts, esters, acids, and mixtures thereof.
48. The method of claim 38, wherein the hyaluronan-based material is an ester comprising from about 50 percent to about 100 percent hyaluronic acid esterification.
49. A method of treating a mammal having a bone defect comprising administering to the site of bone defect an effective amount of a osteogenic composition, wherein the osteogenic composition comprises an osteogenic protein and a hyaluronic acid ester, said composition being in the form of a cylindrical rod.
50. The method of claim 47, wherein the bone defect is osteoporotic or osteopenic bone.
51. The method of claim 47, wherein the osteogenic protein is selected from the group consisting of members of the bone morphogenic protein (BMP) family.

52. The method of claim 49, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-10, BMP-12 and BMP-13.
53. The method of claim 49, wherein the osteogenic protein is BMP-2 or BMP-6.
54. The method of claim 47, further comprising a bone resorption inhibitor.
55. The method of claim 52, wherein the bone resorption inhibitor is a bisphosphonate.
56. The method of claim 53, wherein the bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, EB-1053, etidronates, ibandronate, neridronate, olpadronate, pamidronate, risedronate, tiludronate, YH 529, zolendronate, and pharmaceutically acceptable salts, esters, acids, and mixtures thereof.
57. The method of claim 47, wherein the hyaluronic acid ester is an ester comprising from about 50 percent to about 100 percent hyaluronic acid esterification.
58. The method of claim 47, further comprising an excipient selected from the group consisting of pharmaceutically acceptable salts, polysaccharides, peptides, proteins, amino acids, synthetic polymers, natural polymers, and surfactants.
59. The method of claim 47, further comprising a bone resorption inhibitor and an excipient selected from the group consisting of pharmaceutically acceptable salts, polysaccharides, peptides, proteins, amino acids, synthetic polymers, natural polymers, and surfactants.

60. A method of treating a mammal having a bone defect, wherein the method comprises:

- (a) administering to the site of bone defect an effective amount of an osteogenic composition, wherein the osteogenic composition comprises an osteogenic protein and a hyaluronic acid ester, said composition being in the form of a cylindrical rod; and
- (b) administering to the site of bone defect an effective amount of a bone resorption inhibitor.

61. The method of claim 58, wherein the bone defect is osteoporotic or osteopenic bone.

62. The method of claim 58, wherein the osteogenic protein is selected from the group consisting of members of the bone morphogenic protein (BMP) family.

63. The method of claim 58, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-10, BMP-12 and BMP-13.

64. The method of claim 58, wherein the osteogenic protein is BMP-2 or BMP-6.

65. The method of claim 58, wherein the bone resorption inhibitor is a bisphosphonate.

66. The method of claim 63, wherein the bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, EB-1053, etidronates, ibandronate, neridronate, olpadronate, pamidronate, risedronate, tiludronate, YH 529, zolendronate, and pharmaceutically acceptable salts, esters, acids, and mixtures thereof.

67. The method of claim 58, wherein the hyaluronic acid ester comprises from about 50 percent to about 100 percent hyaluronic acid esterification.
68. The method of claim 58, wherein the osteogenic composition further comprises an excipient selected from the group consisting of pharmaceutically acceptable salts, polysaccharides, peptides, proteins, amino acids, synthetic polymers, natural polymers, and surfactants.
69. The method of claim 58, wherein step (a) is performed prior to step (b).
70. The method of claim 58, wherein step (b) is performed prior to step (a).
71. The method of claim 58, wherein step (a) is performed substantially simultaneously with step (b).